

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
12 August 2004 (12.08.2004)

PCT

(10) International Publication Number
WO 2004/067774 A3

(51) International Patent Classification⁷: **C12Q 1/68**,
G01N 33/50, C07K 14/47, C12N 15/63, A61K 48/00,
38/17

(21) International Application Number:
PCT/EP2004/000539

(22) International Filing Date: 23 January 2004 (23.01.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
03002212.3 31 January 2003 (31.01.2003) EP
03002153.9 3 February 2003 (03.02.2003) EP

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(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,
MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG,
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,
TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM,
ZW.

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), Euro-
pean (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR,
GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK,
TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments

(88) Date of publication of the international search report:
21 October 2004

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: **SINGLE NUCLEOTIDE POLYMORPHISMS AS PREDICTIVE DIAGNOSTICS FOR ADVERSE DRUG REAC-
TIONS (ADR) AND DRUG EFFICACY**

(57) Abstract: The invention provides diagnostic methods and kits including oligo and/or polynucleotides or derivatives, including
as well as antibodies determining whether a human subject is at risk of getting adverse drug reaction after statin therapy or whether
the human subject is a high or low responder or a good or bad metabolizer of statins. The invention provides further diagnostic
methods and kits including antibodies determining whether a human subject is at risk for a cardiovascular disease. Still further the
invention provides polymorphic sequences and other genes.

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C12Q1/68 G01N33/50 C07K14/47 C12N15/63 A61K48/00
A61K38/17

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12Q C07K A61K G01N C12N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS, EMBL, Sequence Search, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>DATABASE EMBL 'Online! 4 June 1995 (1995-06-04), HABETS ET AL.: "Human T-lymphoma invasion and metastasis inducing TIAM1 protein (TIAM1) mRNA, complete cds." XP002279808 Database accession no. HS162961 cited in the application the whole document</p> <p style="text-align: center;">----- -/-</p>	1-5, 7, 9

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

26 May 2004

Date of mailing of the international search report

26.08.04

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	HABETS G G M ET AL: "SEQUENCE OF THE HUMAN INVASION-INDUCING TIAM1 GENE, ITS CONSERVATION IN EVOLUTION AND ITS EXPRESSION IN TUMOR CELL LINES OF DIFFERENT TISSUE ORIGIN" ONCOGENE, BASINGSTOKE, HANTS, GB, vol. 10, no. 7, 6 April 1995 (1995-04-06), pages 1371-1376, XP002039499 ISSN: 0950-9232 figure 1	1-5,7,9
A	HWANG DAVID M ET AL: "A genome-based resource for molecular cardiovascular medicine: Toward a compendium of cardiovascular genes" CIRCULATION, AMERICAN HEART ASSOCIATION, DALLAS, TX, US, vol. 96, no. 12, 16 December 1997 (1997-12-16), pages 4146-4203, XP002197842 ISSN: 0009-7322 cited in the application tables 8,9	1-5,7,9, 11-16
A	EP 1 136 554 A (BAYER AG) 26 September 2001 (2001-09-26) claims 1-15; examples 1-4	1-5,7,9, 11-16
A	OHNISHI Y ET AL: "IDENTIFICATION OF 187 SINGLE NUCLEOTIDE POLYMORPHISMS (SNPS) AMONG 41 CANDIDATE GENES FOR ISCHEMIC HEART DISEASE IN THE JAPANESE POPULATION" HUMAN GENETICS, BERLIN, DE, vol. 106, 2000, pages 288-292, XP002949197 ISSN: 0340-6717 table 1	1-5,7,9, 11-16
A	TURNER S T ET AL: "Antihypertensive pharmacogenetics: Getting the right drug into the right patient" JOURNAL OF HYPERTENSION, CURRENT SCIENCE, PHILADELPHIA, PA, US, vol. 19, no. 1, January 2001 (2001-01), pages 1-11, XP002241062 ISSN: 0263-6352 page 4, paragraphs 2,3 page 7, paragraph 3 - page 8, right-hand column, last paragraph	1-5,7,9, 11-16
	-/-	

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP2004/000539

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>DORNBROOK-LAVENDER KIMBERLY A ET AL: "Genetic polymorphisms in emerging cardiovascular risk factors and response to statin therapy." CARDIOVASCULAR DRUGS AND THERAPY, vol. 17, no. 1, January 2003 (2003-01), pages 75-82, XP009030786 ISSN: 0920-3206 (ISSN print)</p>	

INTERNATIONAL SEARCH REPORT

International application No.

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Box No. I Nucleotide and/or amino acid sequence(s) (Continuation of item 1.b of the first sheet)

1. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, the international search was carried out on the basis of:

a. type of material

☒

a sequence listing

☐

table(s) related to the sequence listing

b. format of material

☒

in written format

☒

in computer readable form

c. time of filing/furnishing

☐

contained in the international application as filed

☒

filed together with the international application in computer readable form

☐

furnished subsequently to this Authority for the purpose of search

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional comments:

INTERNATIONAL SEARCH REPORT

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Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 11 and 12 are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☒ Claims Nos.: 6, 8, 9 (partially), 10
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-16 (all partially)

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claim 11 and 12 are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box II.2

Claims Nos.: 6, 8, 9 (partially), 10

Present claims 6, 8-10 relate to a product (reagent) defined by reference to a desirable characteristic or property, namely its ability to bind to a polypeptide according to the present application and modulate the activity of said polypeptide.

The claims cover all reagents having this characteristic or property, whereas the application does not provide any support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for such reagents. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the reagents by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, no search has been carried out for claims 6, 8 and 10, and claim 9 has been searched with respect to the expression vector of claim 2.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP2004/000539

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
EP 1136554	A	26-09-2001	EP	1136554 A1	26-09-2001
			AU	4419601 A	03-10-2001
			WO	0170810 A2	27-09-2001